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Mechanosensitive GPCRs and ion channels in shear stress sensing

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Abstract

As a universal mechanical cue, shear stress plays essential roles in many physiological processes, ranging from vascular morphogenesis and remodeling to renal transport and airway barrier function. Disrupted shear stress is commonly regarded as a major contributor to various human diseases such as atherosclerosis, hypertension, and chronic kidney disease. Despite the importance of shear stress in physiology and pathophysiology, our current understanding of mechanosensors that sense shear stress is far from complete. An increasing number of candidate mechanosensors have been proposed to mediate shear stress sensing in distinct cell types, including G protein-coupled receptors (GPCRs), G proteins, receptor tyrosine kinases, ion channels, glycocalyx proteins, and junctional proteins. Although multiple types of mechanosensors might be able to convert shear stress into downstream biochemical signaling events, in this review, we will focus on discussing the mechanosensitive GPCRs (angiotensin II type 1 receptor, GPR68, histamine H1 receptor, adhesion GPCRs) and ion channels (Piezo, TRP) that have been reported to be directly activated by shear stress.

Introduction

Among the five basic human senses described by Aristotle [1], both touch and hearing fall into the category of mechanosensation. Besides these self-conscious mechanosensory modalites mediated by the nervous system, shear stress sensing is also a vital part of mechanobiology. In biology, shear stress is defined as the coplanar frictional force due to fluid (e.g., blood, urine, lymph) or air flow in the vascular system, kidney, and lung divided by the cross-sectional area [2]. Although shear stress is generally small in magnitude (typically <70 dyn/cm^2 under physiological conditions) [2], it plays crucial roles in organ

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development and tissue homeostasis. For example, shear stress in a developing embryo is absolutely required for yolk sac vascular remodeling and vasculogenesis. Disrupting the shear stress sensor Piezo1 in mouse causes massive vascular remodeling defects and embryonic lethality [3,4]. Additionally, disturbed or oscillatory shear stress in adults is strongly associated with atherosclerosis, the leading cause of vascular disease worldwide [5].

Many types of cells are capable of sensing shear stress, including vascular endothelial cells, osteocytes and chondrocytes, inner ear hair cells, and epithelial cells. Among them, blood flow-triggered shear stress sensing in vascular endothelial cells is probably the best studied [6]. A complex network of cellular signaling pathways is activated by vascular shear stress, including the integrins/focal adhesion kinase (FAK)/mitogen-activated protein kinases (MAPKs) pathway, the platelet and endothelial cell adhesion molecule 1 (PECAM-1)/VEGFR-2/VE-cadherin/PI3K/AKT pathway, as well as the Gq/11/PLC/calcium signaling pathway [7]. This leads to both short term (vasodilatation) and long term (vascular remodeling and morphogenesis) effects on vascular physiology and pathophysiology [6]. Interestingly, differential flow patterns such as laminar flow, pulsatile flow, and reciprocating flow can induce distinct cellular signaling events, resulting in different physiological outcomes [6]. For instance, constant laminar blood flow is atheroprotective and helps maintain the quiescent state of endothelial cells to reduce inflammation. By contrast, disturbed flow at branch points and other regions of complex geometry is well known to be pro-inflammatory, placing these “hot spots” as high-risk areas for atherogenesis [6].

A central player in shear stress sensing and its mediated physiological and pathophysiological effects is the mechanosensors that detect shear stress. Upon activation by shear stress, these mechanosensors then turn on downstream cellular signaling pathways. Many types of candidate mechanosensors have been proposed to sense shear stress, including G protein-coupled receptors (GPCRs), G proteins, receptor tyrosine kinases, ion channels, glycocalyx proteins that form a polymer meshwork surrounding cells pericellularly, and junctional proteins such as PECAM-1 [8-10]. In the current review, we will focus on the mechanosensitive GPCRs and ion channels that may detect shear stress in different tissues and organs (Figure 1). Notably, these mechanosensors share little sequence homology and exhibit distinct structures (Figure 1), indicating that different types of shear stress sensors might arise independently during evolution. This complexity of shear stress sensors would enable the organisms to cope with distinct shear stress under different conditions.

G protein-coupled receptors (GPCRs)

GPCRs transmit various external and internal cues across the cell membrane. After the original discovery that mechanical force can directly activate angiotensin II type 1 receptor (AT_1R) in an angiotensin II-independent manner [11], many other types of Gq/11-coupled GPCRs have also been reported to sense shear stress, including GPR68 receptor [12], histamine H1 receptor (H_1R) [13], muscarinic M_5 receptor [14], vasopressin V_{1A} receptor [14], bradykinin B_2 receptor [15], sphingosine 1-phosphate receptor [16], dopamine D_5 receptor [17], and endothelin ET_A receptor [14] (Figure 2). However, most of these putative

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mechanosensitive GPCRs have not been verified to directly sense shear stress *in vivo.* Thus, it is important to distinguish whether a putative mechanosensitive GPCR is the direct mechanosensor or an indirect transducer downstream of a mechanosensor.

AT_1R is among the first GPCRs that have been shown to be mechanosensitive in a ligand-independent fashion [11]. Importantly, genetic and pharmacological evidence support that blood pressure overload can induce cardiac hypertrophy *in vivo* by activating AT_1R in an angiotensin II-independent fashion [11]. Mechanistically, force from the membrane causes an anticlockwise rotation of the transmembrane segment 7 (TM7) of AT_1R into the ligand-binding pocket, placing TM7 as a key structural determinant of mechanosensitivity [18]. More recently, GPR68 has been identified as a shear stress sensor through an RNA interference (RNAi) screen [12]. GPR68 is both necessary and sufficient for the shear stress-induced [Ca^{2+}] transients in cell lines [12]. In addition, GPR68 is expressed in the endothelial cells of small-diameter vessels, where it is required for flow-induced [Ca^{2+}] responses [12]. Furthermore, GPR68 knockout mice studies demonstrate that GPR68 plays an important role in small-diameter artery vasodilation and outward remodeling [12]. On the other hand, H_1R is also abundantly expressed in the primary endothelial cells derived from human umbilical veins (HUVEC), where it mediates the shear stress-induced [Ca^{2+}] transients [13]. Similar to GPR68, ectopic expression of H_1R in the otherwise shear stress-insensitive HEK293 cells can make these cells mechanosensitive. Moreover, flow-induced artery vasodilation is greatly reduced in H_1R or its downstream Gq/11 knockout mice, supporting a physiological role of H_1R in sensing shear stress. Interestingly, the C-terminal helix 8 (H8) appears to be a key structural motif of the mechanosensitivity of H_1R, as removing H8 abolishes H_1R mechanosensitivity, whereas transferring H8 to a non-responsive GPCR can confer mechanosensitivity [13]. As a short, amphipathic α-helix parallel to the plasma membrane after TM7, H8 is known to play diverse roles, ranging from receptor dimerization to internalization [19]. Since many GPCRs have an H8 motif, including AT_1R and GPR68, it would be interesting to examine whether the H8 motif also mediates mechanosensitivity in AT_1R and GPR68. Should this be the case, H8 would play a general role in determining whether a GPCR is mechanosensitive.

Besides Gq/11-coupled GPCRs, other types of GPCRs could also be mechanosensitive. For example, Gi/o-coupled D_2R and Gs-coupled adenosine A_{2A} receptor ($A_{2A}R$) have both been shown to be activated by hypoosmotic stimulation [13]. As both D_2R and $A_{2A}R$ have an H8 motif, it is possible that H8 mediates their mechanosensitivity. Moreover, multiple G_{olf}-coupled mammalian odorant receptors can be simultaneously activated by both chemical (odors) and mechanical (liquid flow) stimuli [20,21]. Importantly, heterologous expression of certain odorant receptors in mechano-insensitive cells can confer mechanosensitivity, suggesting a direct mechanosensor role for these odorant receptors [20]. At the physiological level, the mechanosensitivity of odorant receptors might encode airflow information and enhance odorant responses.

More recently, multiple members of the adhesion GPCR (aGPCR) family have been suggested to be mechanosensitive [22]. At least 33 aGPCR are found in mammals, and most of them are orphan receptors with unknown agonists and signaling properties [23]. aGPCRs feature a large extracellular N terminus (300–6000 amino acids) that can interact with

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various extracellular matrix proteins [24]. Notably, a highly conserved HL/T(S) sequence of the GPCR proteolysis site (GPS) is present in the N terminal region of most aGPCRs, where autoproteolysis often occurs to generate a mature bipartite aGPCR consisting of the adhesive N-terminal fragment (NTF) and the C-terminal 7-transmembrane domain fragment (CTF) [24]. It has been suggested that mechanical force could shed the inhibitory NTF off aGPCRs and prime the receptors for ligand-dependent and -independent activation, the so called "tethered agonism model" [22]. Recent cryo-electron microscopy studies support that the tethered agonism model might be a general activation mechanism of aGPCRs [25-28]. After activation, aGPCRs can be coupled to multiple types of G proteins, including Gα12/13, Gαq/11, Gαs, and Gαi/o, depending on the specific receptor and cellular context.

aGPCRs can be activated by distinct forms of mechanical forces, such as shear stress, vibratory shaking, stretch, and touch, indicative of diverse roles of aGPCRs in mechanobiology [9]. Among various putative mechanosensitive aGPCRs, ADGRG1/GPR56 is among the first that have been deorphanized and its known ligands include many extracellular matrix factors, such as collagen III, laminin, heparan sulfate, L-Phenylalanine, CD9/CD81, etc [9]. ADGRG1/GPR56 is widely expressed in many tissues and organs, including the brain, immune system, kidney, pancreases, muscle, testis, and hematopoietic system [29]. In platelets, ADGRG1/GPR56 is activated by collagen and blood flow-induced shear stress [30]. By coupling with Gα12/13 signaling, ADGRG1/GPR56 plays an important role in platelet adhesion and plug formation upon blood vessel injury [30]. It should be noted that although many aGPCRs have been suggested to be mechanosensitive, unlike aforementioned mechanosensitive GPCRs, aGPCRs do not have an H8 motif. Thus, aGPCRs may use a different mechanism to sense mechanical forces.

The seven-transmembrane domain Frizzled receptors are a unique family of GPCRs that interact with Wnt ligands to activate downstream signaling cascades. Depending on the cellular context, Frizzled receptors can mediate both canonical and non-canonical Wnt signaling. Interestingly, Frizzled receptors have been reported to mediate the shear stress-activated β-catenin pathway in endothelial cells, osteocytes, chondrocytes, and mesenchymal stem cells [31]. However, it remains unknown whether Frizzled receptors can directly sense mechanic stimulation, as they lack an H8 motif and β-catenin can also be activated by shear stress in a Frizzled receptor-independent fashion [31].

Piezo channels

Besides GPCRs, ion channels are another major group of mechanosensors in mechanobiology. In fact, since their discovery in 2010 [32,33], the mechanosensitive Piezo channels (Piezo1 and Piezo2) are arguably the best recognized mechanosensors involved in touch, proprioception, mechanical itch, bladder-stretch sensing, baroreception, bone formation, and blood flow-induced shear stress sensing [10,34-36]. As the roles of Piezo channels in sensory biology have been extensively reviewed elsewhere [10,34-36], in this section, we will focus on the shear stress sensing role of Piezo channels, particularly Piezo1.

Piezo1 is expressed in endothelial cells and arterial smooth muscle cells, where it can be activated by blood flow-induced shear stress and membrane stretch [37]. Depending on the

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flow conditions, Piezo1 has complex roles in cardiovascular physiology. Under the normal laminal blood flow condition, calcium influx through the shear stress-activated Piezo1 can activate the proteolytic enzymes calpains, leading to focal adhesion turnover, actin cytoskeleton rearrangement, and endothelial cell alignment in the direction of blood flow [3,4]. Additionally, Piezo1-mediated calcium signaling activates membrane type 1 matrix metalloproteinase (MT1-MMP) in endothelial cells and promotes endothelial sprouting and capillary network formation [3,4,38]. Moreover, shear stress-activated Piezo1 has been shown to elevate the release of the key vasodilator factor nitric oxide (NO) from endothelial cells by phosphorylating endothelial NO synthase (eNOS) at Ser1176 and Ser 320 sites, resulting in vasodilation [39,40]. Collectively, endothelia Piezo1 channel is atheroprotective with laminal blood flow (Figure 3a). In contrast to the vasodilation role of Piezo1, high blood flow due to physical exercise activates Piezo1, which then depolarizes endothelial cells and artery smooth muscle cells and induces mesenteric vasoconstriction [41]. Mechanistically, endothelial cells and artery smooth muscle cells are electrically coupled by gap junctions. The opening of Piezo1 depolarizes endothelial cells, and this high blood flow-induced depolarization is strong enough to be transmitted to artery smooth muscle cells where the voltage-gated $Ca_V1.2$ channels are then activated to trigger vasoconstriction and enhance physical performance [41] (Figure 3b). On the other hand, inner curvatures of the aortic arch are often exposed to turbulent blood flow, where shear stress-activated Piezo1 contributes to endothelial inflammation and atherosclerosis. Under this condition, Piezo1 activation promotes endothelial ATP release, which then activates the Gq/11-coupled $P2Y_2$ receptor in endothelial cells in an autocrine manner [39]. Downstream of Piezo1 and Gq/11 signaling, integrin α5 and FAK are activated to stimulate the NF-κB pathway, resulting in atherogenic inflammation [42] (Figure 3c). Thus, although Piezo1 is atheroprotective under laminar flow, it becomes detrimental under turbulent flow.

The shear stress-sensing role of Piezo1 is not restricted to the vasculature. For example, fluid shear stress is known to activate T cells, and Piezo1 mediates this effect through calcium signaling and its downstream transcription factors NF-κB, NFAT, and AP-1 [43]. Additionally, Piezo1 in red blood cells senses shear stress and regulates cell volume, and gain-of-function mutations of Piezo1 cause the dehydrating red blood cell disease xerocytosis in humans [44,45]. In osteoblasts and chondrocytes, Piezo1 and Piezo2 channels play important roles in bone formation by relaying fluid shear stress and extracellular matrix stiffness signals to NFAT, YAP1, and β-catenin [46]. Furthermore, Piezo1 has been shown to mediate membrane stretch-induced currents in flow shear force-sensing renal epithelial cells and bladder urothelial cells [47-49]. Lastly, Piezo1 is expressed in the tendon cells (tenocytes) and required for their shear stress-induced responses [50]. Intriguingly, Piezo1 promotes tendon stiffness by regulating collagen cross-linking, and a gain-of-function mutation of Piezo1 is associated with enhanced jumping performance in humans [50]. Taken together, as Piezo channels can be activated by shear stress in multiple cell types and tissues, they may function as a universal shear stress sensor.

How is Piezo1 activated by shear stress? Recent structural studies have provided invaluable insights. The trimeric Piezo1 channel features a three-bladed, propeller-like architecture (Figure 1b), with each Piezo1 protomer containing 38 transmembrane segments [51]. Among these 38 TMs, 36 N-terminal TMs form 9 repetitive folding units (blade), whereas

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the last 2 C-terminal TMs constitute the ionic permeation pore [51-54]. As Piezo1 blades curve into dome-shaped membrane areas, the nonplanar configuration of the Piezo blades may directly serve as the mechanosensor of membrane tension and curvature [52,55]. In this regard, the activation mechanism of Piezo channels fits the “force from lipids” model, meaning that the gating force is from the plasma membrane but not the extracellular matrix or intracellular cytoskeleton. Indeed, purified Piezo1 proteins reconstituted into artificial lipid bilayers can be directly activated by an increase in membrane tension [56,57], strongly supporting that Piezo channels are intrinsically mechanosensitive. Nevertheless, the activities of Piezo channels can be greatly influenced by both extracellular matrix and intracellular cytoskeleton. For example, when expressed in HEK293T cells, different extracellular matrix proteins modulate the mechanosensitivity of Piezo1 at distinct shear stress levels. Namely, under the high shear stress condition, fibronectin potentiates Piezo1 channel activity, whereas under the low shear stress condition, collagen type I, III, and laminin sensitizes Piezo1 [58]. On the other hand, the presence of cytoskeleton makes it more difficult to activate Piezo1 in cell-attached patch-clamp recordings, suggesting a negative impact of cytoskeleton on Piezo1 mechanosensitivity [59,60]. Taken together, although Piezo channels are intrinsically gated by the force from lipids, they can also sense the force from tethers. This complex feature of mechanosensitivity might explain why Piezo channels can detect so many different forms of mechanical stimuli.

TRP channels

Several TRP channels have been proposed to function as mechanosensitive ion channels, including TRPV4, TRPA1, TRPC1, TRPC6, TRPN1/NOMPC/TRP-4, and polycystin-2 (also called PKD2 or TRPP1) [61]. However, many of them might act downstream of other mechanosensors and respond indirectly to mechanical stimulation. One exception is the NOMPC subfamily TRP channels TRP-4 and NOMPC, which are *bona fide* mechanosensors in *C. elegans* and *Drosophila,* respectively [62-65]. Nevertheless, they are not present in mammals.

As a hair-like structure extending from the cell surface, primary cilia may directly sense fluid shear stress. In line with this view, left-right asymmetry in most vertebrates is primarily determined at the left-right organizer (LRO) by primary cilia that detect directional fluid flow [66]. TRPP1 has been proposed to act as the mechanosensitive channel that senses fluid shear force-induced bending of the cilium [67]. However, direct activation of TRPP1 by shear stress has not yet been demonstrated. In fact, the main Ca^{2+}-conducting ion channels in primary cilia appear to be the PKD1L1–PKD2L1 heteromeric complexes that do not exhibit any notable mechanosensitivity [68,69]. Additionally, a recent study suggested that TRPP1 mainly conducts monovalent Na^+ and K^+, but not Ca^{2+} [70]. Thus, the mechanosensor in primary cilia requires further investigation.

Recently, both fly and human TRPA1 have been shown to detect shear stress [71,72]. Importantly, TRPA1 can be activated by shear stress in a membrane-delimited and calcium-independent manner [71]. Moreover, ectopic expression of TRPA1 confers shear stress sensitivity to both fly and human cells that are normally insensitive to shear stress [71]. Combined, these results strongly suggest that TRPA1 is a direct sensor of shear stress.

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Interestingly, TRPA1 appears to be selectively activated by shear stress but not stretch or touch [71], which probably places TRPA1 as the only known mechanosensitive ion channel that is specifically activated by shear stress, but not other forms of mechanical stimuli. Mechanistically, shear stress activates TRPA1 by enhancing membrane fluidity (Figure 4), as decreasing membrane fluidity can largely suppress TRPA1-mediated shear stress response whereas chemicals that increase membrane fluidity can activate TRPA1 without shear stress [71]. At the physiological level, shear stress-activated TRPA1 mediates a nociceptive behavior and intestinal stem cell proliferation in *Drosophila* [71,72], while its potential roles in mammalian shear stress sensing require further investigation. Since TRPA1 knockout mice have been previously developed to study its potential roles in pain sensation [73,74], re-examining these mice might reveal a novel role of TRPA1 in mammalian fluid shear stress sensing.

Conclusions and perspectives

Fluid (blood, urine, lymph) and air flows inside the body are vital for our survival because they carry nutrients and oxygen and remove wastes. Shear stress is a universal cue for many cell types exposed to fluid or air flow, most of which are non-excitable cells (e.g., endothelial cells, osteocytes and chondrocytes, and epithelial cells). As a result, shear stress-induced mechanical responses are typically slow, and shear stress sensing is mostly interoceptive and sometimes could go unnoticed, which may partially explain why physicians often call atherosclerosis induced by disturbed shear stress a silent killer.

Cells typically employ various membrane proteins to detect extracellular physical and chemical cues. Compared to many classical signaling pathways initiated by other physical and chemical cues, a major difference in shear stress-evoked signaling is that a host of different types of membrane proteins may serve as shear stress sensors. For example, animals mainly use TRP channels to detect temperature cues and GPCRs to sense odors. However, different types of GPCRs, G proteins, ion channels, junctional proteins, glycocalyx proteins, receptor tyrosine kinases, and integrins have all been suggested to sense shear stress [8]. This may represent the complex nature of shear stress that cells experience under different flow conditions. Nevertheless, whether the aforementioned candidate shear stress sensors all function as a *bona fide* mechanosensor to directly sense shear stress remains to be determined. There are several challenges surrounding the verification of a candidate shear stress sensor as a force-sensing mechanoreceptor. First, it is difficult to establish the specificity of a shear stress sensor, as nearly all proposed candidate proteins are also activated by other mechanisms, such as ligand binding, membrane potential, receptor trafficking, etc. Second, shear stress levels may vary greatly *in vivo,* depending on the location and duration, which makes it difficult to establish a standardized experimental condition for studying shear stress sensors. Third, many candidate shear stress sensors may have functional redundancy, especially GPCRs. Lastly, there are currently no universally accepted criteria for verifying shear stress sensors. For mechanosensitive channels, besides overexpression in heterologous expression systems, they are often reconstituted in artificial liposomes to provide definitive evidence on their intrinsic mechanosensitivity. However, it is difficult to apply a similar strategy to non-channel types of candidate shear stress sensors, as the functional readout of these candidates may not be as straightforward

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as electrophysiological recordings of ion channels. Further research is clearly needed to address these challenges.

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Data availability

No data was used for the research described in the article.

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* of special interest

* * of outstanding interest

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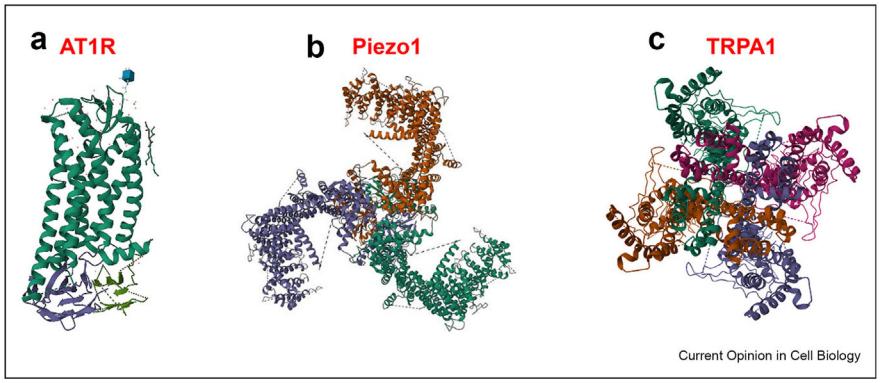

Figure 1.

Atomic structures of representative mechanosensitive GPCRs and ion channels. Many different types of membrane proteins have been suggested to act as shear stress sensors, and shown are the structures of some representative GPCR and ion channels. **(a)** The structure of nanobody-stabilized angiotensin II type 1 receptor (AT_1R) [75]. The H8 helix may be a key structural motif for the mechanosensitivity of AT_1R. **(b)** Structure of the trimeric Piezo1 channel [51-53]. Blades formed by its N-terminal TMs may directly sense membrane tension. **(c)** Structure of full-length human TRPA1 channel [76], which can be activated by shear stress in a membrane-delimited and calcium-independent manner [71].

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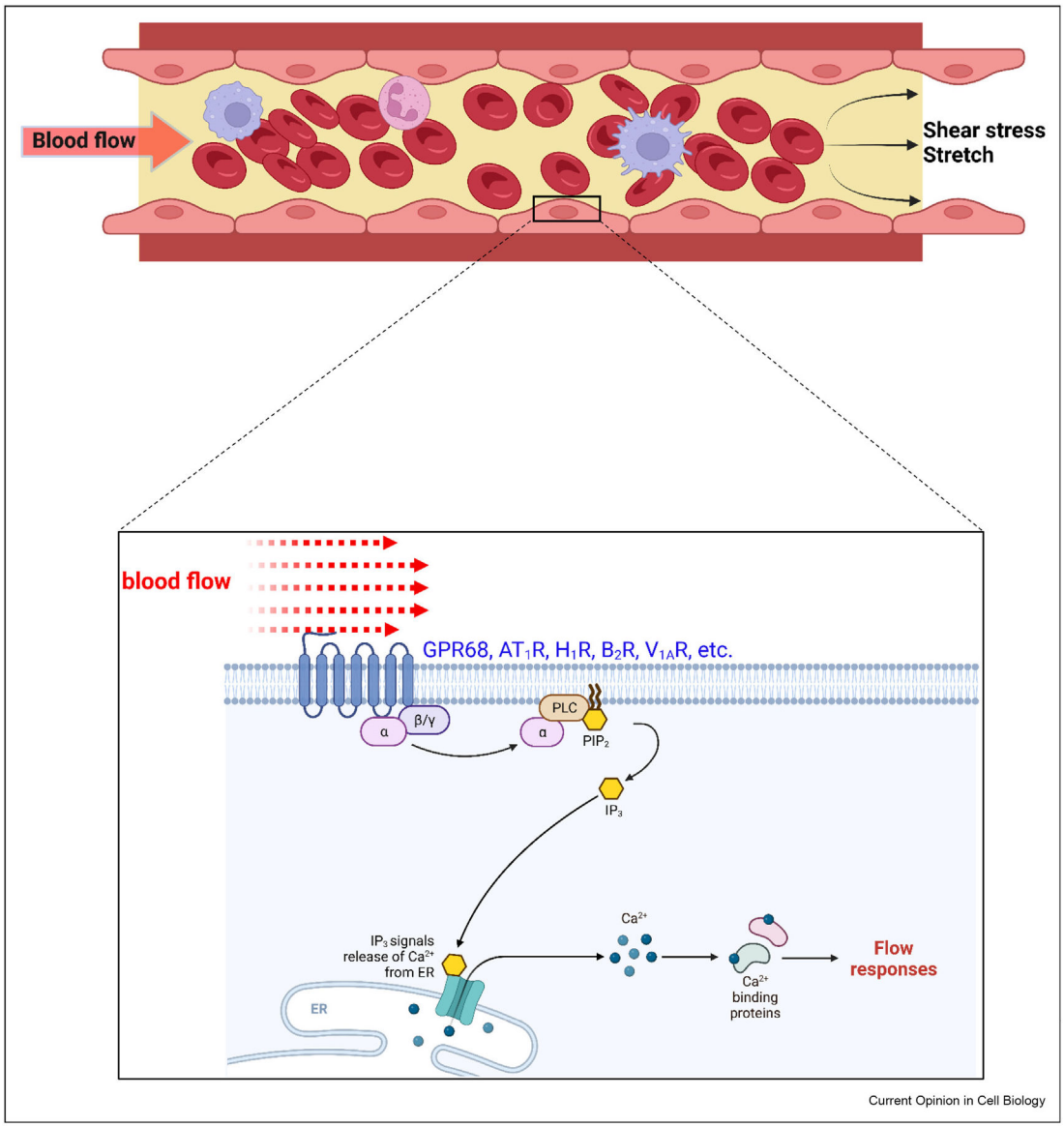

Figure 2.

GPCRs involved in shear stress sensing. Many types of GPCRs may sense shear stress. Shown are the signaling pathways downstream of shear stress-activated, Gq/11-coupled GPCRs.

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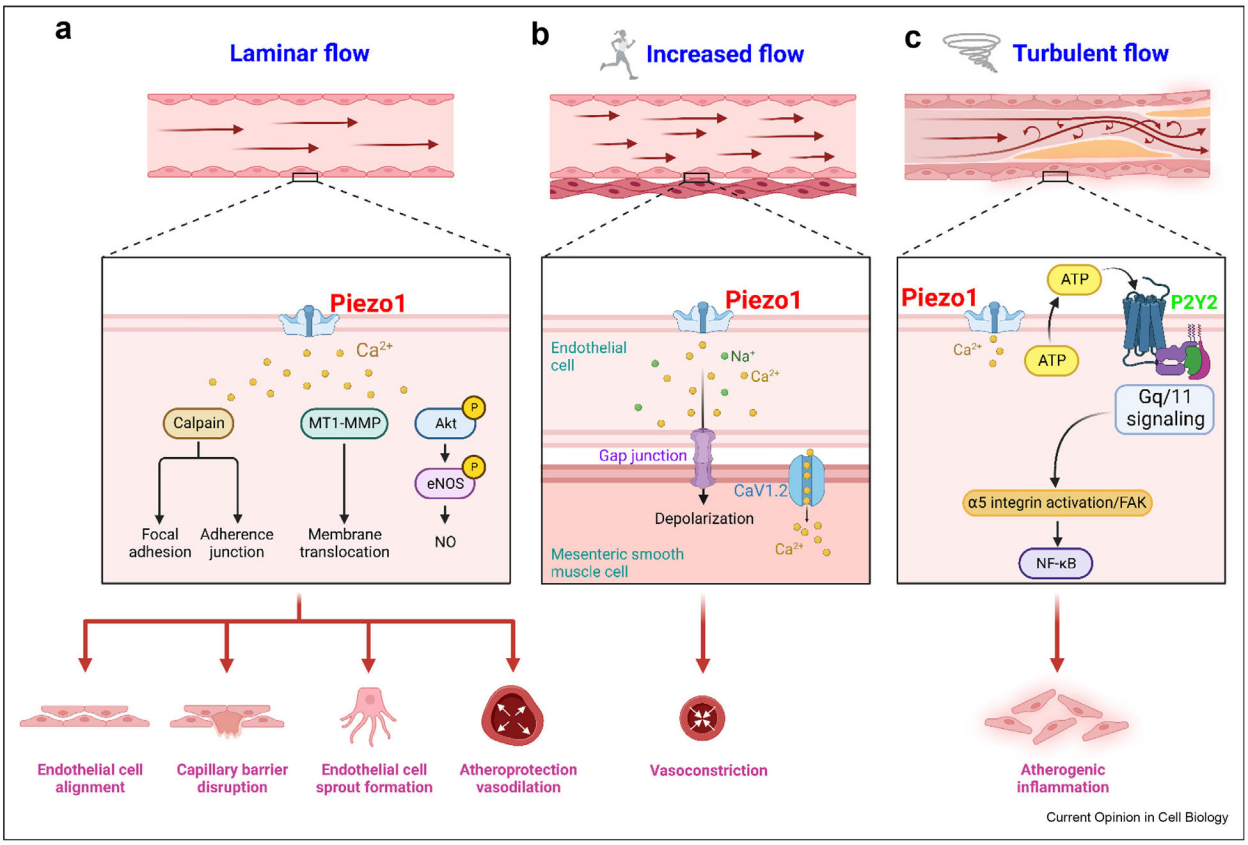

Figure 3.

Piezo1 plays an essential role in sensing shear stress under different conditions. **(a)** Laminar flow-induced Piezo1 activation is atheroprotective and promotes vasodilation. Shown are the signaling pathways downstream of laminar flow-activated Piezo1. **(b)** Increased blood flow during physical exercise activates Piezo1 and triggers vasoconstriction due to the electric coupling between endothelial cells and mesenteric smooth muscle cells. **(c)** Turbulent blood flow activates Piezo1 and triggers atherogenic inflammation.

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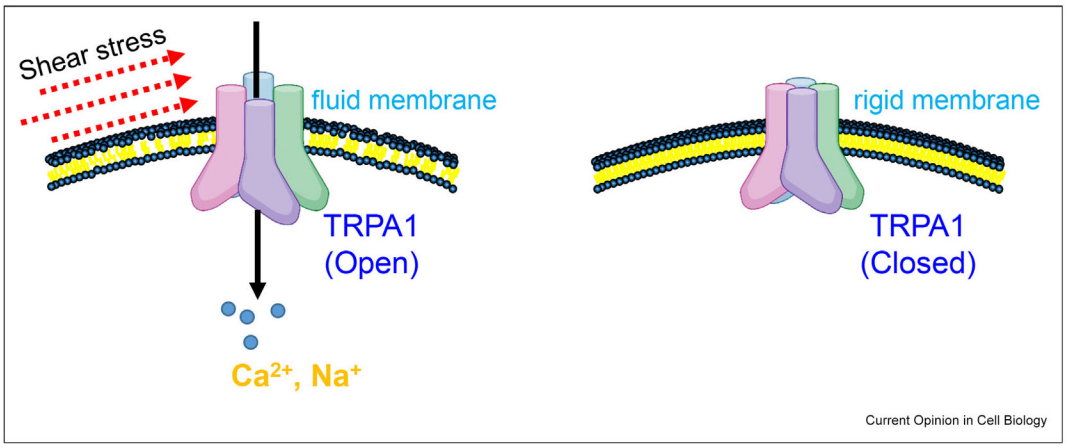

Figure 4.

Shear stress activates TRPA1 by enhancing membrane fluidity. Both fly and human TRPA1 can be activated by shear stress through enhanced mem-brane fluidity. Upon shear stress, the plasma membrane becomes more fluid and less organized. Importantly, shear stress activation of TRPA1 does not require any intracellular signaling, supporting a direct activation mechanism by shear stress.